

REMARKS/ARGUMENTS

Claims 1-118 and 133-139 are pending, claims 29-32 are objected to, and claims 1-49, 52, 54, 64-115, 118, and 133-139 stand rejected in this application. Applicants reserve the right to prosecute the originally filed claims, including previously withdrawn claims 50, 51, 53, 55-63, 116, 117 (potentially misidentified as withdrawn by Examiner), and 119-132, in the future. Claims 1, 3-5, 7, 8, 10-17, 20, 22-24, 29-32, 48, 68-70, 75-76, 84, 85, 92, 93, 98-100, 103, 108, 110, 111, 118, 133, 135 and 138 have been amended, and no new matter was introduced by these amendments. Claims 2, 6, 27, 134, and 139 have been canceled herein. The proposed amendments to the claims and the comments in the office action regarding claims 1-49, 52, 54, 64-115, 117, 118, and 133-139 are now addressed in turn.

Interview Summary

Applicants thank Examiner Whaley and Examiner Moran for the telephonic interview held on Tuesday, October 17, 2006. The objections to claims 29-32 and the claim rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, 1st and 2nd paragraphs were discussed. The Examiners agreed that the draft amendments to the claims proposed by the Applicant overcame the objections to claims 29-32, the non-statutory subject matter rejection of claims 138 and 139 under 35 U.S.C. § 101, the lack of utility rejection under 35 U.S.C. § 101 for at least claim 1, the 35 U.S.C. § 112, first paragraph rejection of at least claim 1, and the 35 U.S.C. § 112, second paragraph rejection of at least claim 92. The Examiners and Applicants further discussed the draft amendments to overcome the U.S.C. § 112, second paragraph rejections of claims 68, 84, and 99, and agreed that “another” was preferable to “further” in the claims. The only art rejection that was discussed was the rejection of claim 16 as being allegedly made obvious by Fan et al. in view of Webster et al. and Kellam et al. Although the claim was not included in the listing of rejected claims, it was included in the detailed explanation of the rejection. The Examiners confirmed that claim 16 was being rejected in

light of the cited art. No other aspects of this or any other rejection under 35 U.S.C. § 103 were discussed.

Applicant's Election

Examiner's discussion regarding Applicant's election with traverse of Group I (Claims 1-118 and 133-139) in the reply filed on 03/24/2006 is acknowledged. In addition, Applicants believe that the listing of claim 117 as a "withdrawn" claim in the Office Action of July 19, 2006 is incorrect. As noted by the Examiner, Applicants elected "Specie C (drawn to mean intensities based on trimmed means, as recited in instant claims 54, 111, and 117)." However, the Office Action also identified claim 117 in the listing of claims withdrawn. In view of the election filed March 24, 2006 and the Office Action mailed July 19, 2006, Applicants believe that claim 117 was not withdrawn by the Applicant's election and therefore have used the status identifier "original" in the listing of claims submitted herewith. Applicants respectfully request clarification of this matter.

Objections

Claims 29-32 were objected to because they were deemed to be grammatically incorrect. Applicants have amended claims 29-32 by substituting the word "centimeter" for the word "centimeters." No new matter was introduced by virtue of these amendments, Applicants believe the objections to claims 29-32 have been rendered moot and respectfully request that they be withdrawn.

Claim Rejections Under 35 USC § 101

Claims 1-49, 52, 54, 64-115, and 118 were rejected under 35 U.S.C. § 101 as being allegedly drawn to non-statutory subject matter. In particular, the Office Action alleged that "no actual, concrete result is recited in the claims, nor is any useful result "produced" in a tangible form useful to one skilled in the art." In order to further clarify the claimed invention,

Applicants have amended claims 1 and 118 to include the step of “outputting a result of said analyzing...” This amendment adds no new matter as it is fully supported by the specification as originally filed, e.g., in paragraphs [00104]-[00107], and makes clear the concrete, tangible, and useful result of the claimed invention. As such, Applicants believe that the rejections have been overcome and respectfully request reconsideration and withdrawal of the rejections of claims 1 and 118, and all claims dependent thereon, under 35 U.S.C. § 101.

With regards to claim 108, Applicants respectfully traverse the instant rejection. Contrary to what is stated in the Office Action, claim 108 is not directed to inputting allele frequency measures into a computer system and analyzing data in the computer system. Claim 108, as originally filed, is drawn to “A method for determining a relative allele frequency for an interrogation position in a group of individuals.” As such, Applicants believe that the rejection is based on a simple misreading of the instant claim, and respectfully request reconsideration and withdrawal of this rejection of claim 108 and all claims dependent thereon.

Claims 138-139 were rejected under 35 U.S.C. § 101 as being allegedly drawn to non-statutory subject matter. Applicants have amended claim 138 to be drawn to a computer program product comprising a machine readable medium on which is provided program instructions for characterizing a position in a nucleic acid segment, comprising: code for determining first and second measures of relative allele frequency in a first and second sample, respectively, and code for analyzing the first and second measures to characterize the interrogation position. No new matter was entered by virtue of this amendment, which is fully supported in the specification as originally filed, e.g., in paragraphs [0087]-[0095], and in particular in paragraphs [0087], [0088], and [0090]. Applicants believe that the amendments to claim 138 overcome the instant rejection and respectfully request that the rejection be withdrawn.

Lack of Utility

Claims 1-5, 17-49, 52, 54, 64-74, 77, 108-115, 118, 133, and 138 were rejected under 35 U.S.C. § 101 because the claimed invention was allegedly not supported either by a well-asserted utility or a well-established utility. Claims 1-5, 17-49, 52, 54, 64-74, 77, 108-115, 118, 133, and 138 were also rejected under 35 U.S.C. § 112, first paragraph, because the claimed invention was allegedly not supported either by either a specific, substantial, and credible asserted utility or a well established utility.

Applicants have amended claims 1, 133, and 138 to include the limitation of claims 6, 134, and 139, respectively, that the interrogation position is characterized as being associated with a phenotypic characteristic/trait of interest. No new matter was introduced by virtue of the amendments, since this limitation is fully supported by the claims as originally filed. For claims 1, 133 and 138, the corresponding dependent claims (claims 6, 134, and 139) have been canceled herein. (In addition, all claims previously depending from claim 6 were amended to depend from claim 1.) In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection of claims 1, 133, and 138, and all claims dependent thereon.

With regards to claim 108, Applicants respectfully disagree. The Office Action states, “The instant claims recite a general method of ‘characterizing an interrogation position’ in a nucleic acid segment.” Applicants respectfully point out that Claim 108, as originally filed, does not recite “characterizing an interrogation position,” but instead is drawn to “A method for determining a relative allele frequency for an interrogation position in a nucleic acid segment...” The determination of relative allele frequencies is a useful outcome of the claimed method that would be readily apparent to one of ordinary skill in the art. However, to further clarify the claimed invention Applicants have amended the claim to recite, “A method for determining a relative allele frequency for an interrogation position in a *pool of* nucleic acid segments...” This amendment further clarifies that a utility of the claimed invention is determination of a relative allele frequency for an interrogation position in a pool of nucleic

acid segments, and Applicants respectfully submit that this utility would be readily considered specific, substantial, and credible to one of ordinary skill in the art. No new matter was introduced by the instant amendment, which is fully supported by the specification as originally filed, e.g., in paragraphs [0067]-[0073] and [0079]-[0083]. As such, Applicants request withdrawal of the instant rejection of claim 108 and all claims dependent thereon.

With regards to claim 118, Applicants respectfully point out that the claim as originally filed recites, “analyzing in the computer system the first measure and the second measure to characterize the polymorphic marker as being associated with a phenotypic trait of interest.” As such, Applicants believe that the utility of the claimed method would be clear to one of skill in the art as originally filed. However, in the interest of expediting prosecution of the instant application, Applicants have amended claim 118 to recite, “A computer-implemented method for characterizing a polymorphic marker in a nucleic acid as being associated with a phenotypic trait of interest” in the preamble, and corrected antecedent basis in the last line of the claim. Since association with a phenotypic trait of interest was an element of the claim as originally filed, no new matter was introduced by virtue of the amendment. As such, Applicants, respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 USC § 112 2nd Paragraph

Claims 68, 70-71, 77, 79, 84-85, 89-93, 99-100, and 138 were rejected under 35 USC § 112, 2nd paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter with Applicant regards as the invention.

With regards to claim 68, the terms “further first measure” and “further second measure” were alleged to be unclear. To further clarify the instant invention, Applicants have substituted the term “another first measure” for the term “further first measure,” and have substituted the term “another second measure” for the term “further second measure.” This amendment adds no new matter and is completely supported by originally-filed application

since the amendment does not change the meaning or scope of claim 68. Applicants respectfully request reconsideration and withdrawal of the instant rejection of claim 68.

Similarly, claims 84 and 99 recite the limitation “a further plurality” and the Action alleges that this term is unclear and is subject to different interpretations. To further clarify the claimed invention, Applicants have substituted the term “another plurality” for the term “a further plurality” in claims 84 and 99, as well as claims 85 and 100, which depend from 84 and 99, respectively. These amendments add no new matter and are completely supported by the claims as originally filed since they do not change the meaning or scope of the amended claims. Applicants respectfully request reconsideration and withdrawal of the instant rejection of claims 84, 85, 99, and 100.

In addition, to further clarify the claimed invention, Applicants amended claim 93 to substitute the term “additional interrogation positions” for the term “further interrogation positions.” This amendment incorporates no new matter and is fully supported by claim 93 as originally filed. Accordingly, Applicants respectfully request that the instant rejection of claim 93 be withdrawn.

With regards to claim 70, it was alleged that the limitation “the first equation is constrained by a second equation” was unclear. In order to further clarify the claimed invention, Applicants have amended claims 69 and 70. Claim 69 was amended to substitute the term “solving” for the term “applying,” and the phrase “in haplotype pattern j ” was added between “position i ” and “matches a reference allele.” Claim 70 was amended to recite “the corrected relative allele frequencies, P_i , are constrained.” These amendments are fully supported by the instant application, e.g., in paragraph [00211]. Applicants believe that the instant rejections of claims 70 and 71 have been overcome and respectfully request their withdrawal.

It was further alleged that claim 92 recites the limitation “using an equation of the form $N_1 + N_2 - 2$ ” and depends from claim 89, which does not recite or define N_1 and N_2 , rendering the intended meaning of these variables unclear. Applicants have amended claim 92

to depend from claim 91, which does recite and define N_1 and N_2 . This amendment is fully supported in paragraph [00167] of the instant specification. As such, Applicants believe that the instant rejection of claim 92, and all claims dependent thereon, has been rendered moot and respectfully request its withdrawal.

Finally, Applicants respectfully point out that although the Office Action identified claims 77, 79, 89-91, and 138 as being rejected under 35 U.S.C. § 112, second paragraph, the Examiner provided no basis for these rejections as required by MPEP 706.03. As such, Applicants respectfully request clarification or withdrawal of the instant rejections of claims 77, 79, 89-91, and 138.

Claim Rejections Under 35 USC § 103

Claims 1-7, 10, 11, 14-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, 109, 111-114, and 133-139 were rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Fan *et al.* (Genome Research, 2000, Vol. 10, p. 853-860) in view of Webster *et al.* (US 2002/0183933, Filed: Mar. 28, 1997) and Kellam *et al.* (Antimicrobial Agents and Chemotherapy, 1994, Vol. 38, No. 1, p. 23-30).

Applicants respectfully traverse all of the above rejections. In order for a reference or a combination of references to support a *prima facie* case of obviousness, they must (a) disclose all elements of the claimed invention, (b) suggest or motivate one of skill in the art to combine or modify those elements to yield the claimed combination, and (c) provide a reasonable expectation of success should the claimed combination be carried out. Applicants respectfully submit that the cited references fail to teach the claimed invention since they do not disclose all elements of the claimed invention for the reasons that follow.

Applicants have amended claim 1 to further clarify that which Applicants regard as the invention by incorporating limitations from originally-filed claims 2 and 6 (both of which are canceled herein). Claim 1, as currently amended, teaches a method for characterizing an interrogation position that comprises inputting into a computer system a first measure of

relative allele frequency at an interrogation position in a nucleic acid segment derived from a first sample collected from a case group of individuals, and a second measure of relative allele frequency at the interrogation position in a nucleic acid segment derived from a second sample collected from a control group of individuals, analyzing in the computer system the first and second measures, and outputting a result of the analyzing that characterizes the interrogation position as being associated with the phenotypic characteristic of interest.

Although Fan *et al.* do describe a method of genotyping SNPs using oligonucleotide arrays, Fan *et al.* do not teach determining relative allele frequencies in a case group and a control group, analyzing the relative allele frequencies in a computer system, nor outputting a result that characterizes an interrogation position as associated with a phenotypic characteristic of interest, as is taught by the instant claim 1. In contrast, the genotyping of Fan *et al.* was performed for a *single* group of 44 individuals (p. 858, column 1, first full paragraph) who were *not* identified as coming from a case or a control group. As such, Fan *et al.* cannot teach the method of claim 1 since claim 1 recites a first measure of relative allele frequency measured from a case group and a second measure of relative allele frequency measured from a control group and Fan *et al.* does not provide a case and control group, and therefore cannot provide measures of relative allele frequency from case and control groups, the analysis of these measures in a computer system, nor outputting a result that characterizes the interrogation position as being associated with a phenotypic characteristic of interest.

In order to overcome the deficiencies of the primary reference, the Examiner has combined Fan *et al.* with Webster *et al.* and Kellam *et al.* However, these references also do not teach inputting measures of relative allele frequencies from case and control groups into a computer system, analyzing the measures to characterize an interrogation position, and outputting a result characterizing the interrogation position as being associated with the phenotypic characteristic of interest. Although Webster *et al.* does describes a method that utilizes oligonucleotide arrays and nucleic acid samples, the methods of Webster *et al.* determine changes in gene expression in “a sample” and compare the measured expression

level to a *baseline* level (see, e.g., Abstract, [0011], [0013], and [0014]) in sharp contrast to the methods of the present invention, which analyze relative allele frequencies from case and control groups. In addition, Webster *et al.* does not characterize an interrogation position as being associated with a phenotypic characteristic, as do the claims of the instant application. Likewise, Kellam *et al.* do not teach inputting measures of relative allele frequency into a computer system, analyzing the measures to characterize an interrogation position, or outputting a result characterizing the interrogation position as being associated with a phenotypic characteristic of interest. Rather, Kellam *et al.* describes “a new virus sensitivity assay that makes use of genetic recombination to produce virus stocks for sensitivity testing.” (p. 24, column 1, first full paragraph). While it is true that Kellam *et al.* are studying a phenotypic characteristic of interest (resistance to HIV treatment), Applicants find no similarities between the methods of Kellam *et al.* and the methods of the rejected claims. Therefore, Applicants submit that the combination of Fan *et al.*, Webster *et al.*, and Kellam *et al.* does not render the instant invention obvious and Applicants respectfully request withdrawal of the instant rejection of claim 1 and all claims dependent thereon.

With regards to claim 14, neither Fan *et al.*, Webster *et al.*, nor Kellam *et al.* teach a method “wherein the number of individuals in the case group, n, and the number of individuals in the control group, m, each *independently varies* between 10 and 100,000.” Although Fan *et al.* does describe genotyping a group of 44 individuals, these individuals are not subdivided into *case and control groups* whose numbers *independently vary* between 10 and 100,000. Likewise, neither Webster *et al.* nor Kellam *et al.* teach case and control groups containing numbers of individuals that independently vary between 10 and 100,000 since neither teaches case and control groups. As such, the cited references do not teach each and every aspect of the claimed invention and therefore do not present a *prima facie* case of obviousness. As such, Applicants respectfully request withdrawal of the instant rejection of claim 14.

With regards to claim 16, neither Fan *et al.*, Webster *et al.*, nor Kellam *et al.* teach a method “wherein a genetic region containing the SNP position was not previously known to be associated with the phenotypic characteristic of interest.” In fact, Fan *et al.* clearly states, “we developed genotyping assays for a subset of the 874 SNPs that were identified recently in a large-scale polymorphism screen of 75 hypertension candidate genes.” Therefore, the SNPs genotyped by Fan *et al.* were actually in genetic regions previously **known** to be associated with a hypertension phenotype, which actually seems to contradict the method of claim 16. The disclosures of Webster *et al.* and Kellam *et al.* do not overcome this deficiency in the primary reference, and, therefore, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

In addition, the Office Action alleges that a description of “observed versus known allele frequency estimation based on SNPs at the interrogation position using a reference allele ‘C’” in Fan *et al.* is a teaching for the limitation of claim 48. Applicants respectfully point out that claim 48 does not describe a comparison of *observed* and *known* allele frequencies, but rather teaches that the measure of relative allele frequency is the proportion of either the reference or alternate allele at the interrogation position. There is no comparison of observed and known allele frequencies, so Applicants respectfully submit that the rejection is improperly based on a simple misreading of the claim and respectfully request its reconsideration and withdrawal.

Claim 108, as currently amended, is drawn to a method of determining a relative allele frequency for an interrogation position that comprises “determining a plurality of intensities of signals” from reference and alternate nucleic acid segments and using these pluralities of intensities of signals to calculate an equation of the form: “ $\frac{\langle I_{R,1-i} \rangle}{(\langle I_{A,1-j} \rangle + \langle I_{R,1-i} \rangle)}$ or $\frac{\langle I_{A,1-j} \rangle}{(\langle I_{A,1-j} \rangle + \langle I_{R,1-i} \rangle)}$, where $\langle I_{R,1-i} \rangle$ is the average of the plurality of intensities of signals from the reference nucleic acid segment, and $\langle I_{A,1-j} \rangle$ is the average of intensities of signals from the alternate nucleic acid segment.” None of the cited references teach a method of determining a relative allele frequencies that comprises computing an equation that

comprises averages of pluralities of intensities of signals from reference and alternate nucleic acid segments. At best, on page 859, column one, first paragraph, Fan *et al.* provide an equation: “[fluorescein/(fluorescein+phycoerythrin)],” but do not teach that the values in this equation are averages of pluralities of intensities of signals, as is taught by claim 108. As such, the cited references do not teach every element of the claimed invention and therefore do not present a *prima facie* case of obviousness. In light of the foregoing, Applicants respectfully request withdrawal of the instant rejection of claim 108 and all claims dependent thereon.

Claim 133, as currently amended to incorporate limitations from originally-filed claims 2, 6, and 134 (all canceled herein) is drawn to a data processing apparatus comprising a storage device holding computer readable code that includes “computer code which determines a first measure of relative allele frequency at the interrogation position ... derived from a first sample collected from a case group ... wherein the individuals in the case group are selected based on a phenotypic characteristic of interest,” “computer code which determines a second measure of relative allele frequency at the interrogation position ... derived from a second sample collected from a control group ... wherein the individuals in the control group are selected based on lack of the phenotypic characteristic of interest,” and “computer code which analyzes the first measure and the second measure to characterize the interrogation position as being associated with the phenotypic characteristic of interest.” As described in detail above, none of the cited references teaches determining first and second measures of relative allele frequencies for an interrogation position that are derived from first and second samples collected from case and control groups of individuals, respectively, nor do they teach analyzing the measures to characterize an interrogation position as being associated with a phenotypic characteristic of interest. Therefore, since the measures themselves are not taught and the characterization of the interrogation position as associated with the phenotypic characteristic of interest is also not taught, none of the cited references can describe code that determines and analyzes these measures to characterize the

interrogation position as associated with the phenotypic characteristic of interest.

Accordingly, Applicants respectfully request that the instant rejection of claim 133 and all claims dependent thereon, be withdrawn.

Claim 138, as currently amended by incorporation of limitation of originally filed claims 2, 6, and 139 (all canceled herein), provides a “computer program product comprising a machine readable medium on which is provided program instructions for characterizing an interrogation position” that comprises “code for determining a first measure of relative allele frequency at the interrogation position ... derived from a first sample collected from a case group ... wherein the individuals in the case group are selected based on a phenotypic characteristic of interest ... determining a second measure of relative allele frequency at the interrogation position ... derived from a second sample collected from a control group ... wherein the individuals in the control group are selected based on lack of the phenotypic characteristic of interest ... and analyzing the first measure and the second measure to characterize the interrogation position as being associated with the phenotypic characteristic of interest.” As noted for claim 133 above, none of the cited references, whether alone or in combination, teaches determining first and second measures of relative allele frequencies for an interrogation position that are derived from first and second samples collected from case and control groups of individuals, respectively, nor do they teach analyzing the measures to characterize an interrogation position as being associated with a phenotypic characteristic of interest. Therefore, since the measures themselves are not taught and the characterization of the interrogation position as associated with the phenotypic characteristic of interest is also not taught, none of the cited references can describe code that determines and analyzes these measures to characterize the interrogation position as associated with the phenotypic characteristic of interest. Accordingly, Applicants respectfully request withdrawal of the instant rejection of claim 138.

Finally, in order to further expedite prosecution of the instant application, Applicants have amended claims 1, 108, 133 and 138 to add the limitation of claim 27, which states that

the interrogation position contains a biallelic polymorphism (and is canceled herein). This claim was not rejected as allegedly being made obvious by Fan *et al.* in view of Webster *et al.* and Kellam *et al.* As such, Applicants believe that the rejections of claims 1-7, 10, 11, 14-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, 109, 111-114, and 133-139 have been rendered moot by virtue of the amendment and respectfully request that they be withdrawn.

Claims 1, 3-6, 48, 52, 75, 77, 79-81, 83, 84, 86-90, 98-100, 103, 104, 108, 109, 111-113, 135, and 136 were rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Germer *et al.* (Genome Research, 2000, Vol. 10, p. 258-266) in view of Webster *et al.* (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll *et al.* (Nucleic Acids Research, 2002, Vol. 30, No. 11, p. 1-6). Applicants respectfully traverse all of the above rejections. Applicants respectfully submit that the cited references fail to teach the claimed invention since they do not disclose all elements of the claimed invention for the reasons that follow.

Claim 1 as currently amended incorporates limitations of claims 2 and 27, as described above. Neither claim 2 nor claim 27 was rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Germer *et al.* in view of Webster *et al.* and Kroll *et al.* For example, none of these references, whether alone or in combination, teaches inputting measures of relative allele frequencies from case and control groups into a computer system, analyzing the measures to characterize an interrogation position that is a biallelic polymorphism, and outputting a result characterizing the interrogation position as being associated with the phenotypic characteristic of interest. Therefore, Applicants believe that the instant rejection of claim 1 and all claims dependent thereon has been rendered moot by virtue of the amendments to claim 1 and respectfully request its withdrawal.

Similarly, Claim 108 as currently amended incorporates limitations of claims 2 and 27, as described above. Neither claim 2 nor claim 27 was rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Germer *et al.* in view of Webster *et al.* and Kroll *et al.*. In addition, none of the cited references teach a method of determining relative allele

frequencies that comprises computing an equation that comprises averages of pluralities of intensities of signals from reference and alternate nucleic acid segments. Therefore, the cited references do not teach each and every element of the claimed invention, and Applicants respectfully request withdrawal of the instant rejection of claim 108 and all claims dependent thereon.

With regards to claims 135 and 136, Applicants believe the rejections of these claims are improper because both claims depend from claim 133, which was not subject to the instant rejection. With regards to claim 133, none of the cited references teaches determining first and second measures of relative allele frequencies for an interrogation position that are derived from first and second samples collected from case and control groups of individuals, respectively, nor do they teach analyzing the measures to characterize an interrogation position as being associated with a phenotypic characteristic of interest. Therefore, since the measures themselves are not taught and the characterization of the interrogation position as associated with the phenotypic characteristic of interest is also not taught, none of the cited references can describe code that determines and analyzes these measures to characterize the interrogation position as associated with the phenotypic characteristic of interest. At best, Germer *et al.* describes SNP allele-frequency determination by kinetic PCR, but does not provide a method for determining first and second measures of relative allele frequencies that correspond to a case group and a control group, wherein the individuals in the case and control groups are selected based on a phenotypic characteristic of interest. The Office Action points to Figure 1 and Table 1 for allegedly disclosing the claimed invention, but Applicants respectfully point out, "Figure 1 shows kinetic growth curves for two separate PCR reactions (four replicates of each) performed on a sample of DNA" (p. 259, column 2, first full paragraph). So, the two curves in the figure do not correspond to analysis of a case and control population as taught by the instant invention but instead correspond to two PCR reactions for a *single* sample. Similarly, Table 1 presents results of experiments to demonstrate that the kinetic PCR method is valid over a range of allele frequencies, but no

case or control groups were used to generate the information presented therein. In light of the foregoing, Applicants respectfully submit that since the cited references do not teach each and every element of claim 133, they cannot teach the methods of claims 135 and 136, which depend from claim 133, and therefore request reconsideration and withdrawal of the instant rejection of claims 135 and 136.

Claims 1-6, 11-13, 17-19, 22, 23, 26-28, 52, 64-68, 72, 75-77, and 133-139 were rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Barcellos *et al.* (Am. J. Hum. Genet., 1997, Vol. 61, p. 734-747) in view of Webster *et al.* (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll *et al.* (Nucleic Acids Research, 2002, Vol. 30, No. 11, p. 1-6). Applicants respectfully traverse all of the above rejections and submit that the cited references fail to teach the claimed invention since they do not disclose all elements of the claimed invention for the reasons that follow.

Claim 1, as currently amended, is directed to a computer-implemented method for characterizing an interrogation position containing a biallelic polymorphism as being associated with a phenotypic characteristic of interest, and the method comprises inputting into a computer system first and second measures of relative allele frequency at the interrogation position derived from first and second samples collected from case and control groups, respectively; analyzing in the computer system the first and second measures; and outputting a result that characterizes the interrogation position as being associated with the phenotypic characteristic of interest. The Office Action alleges that Barcellos *et al.* describe “estimation of allele frequencies in patients and controls” and that such estimation is a teaching for the first and second measures as in instant claim 1. Applicants respectfully disagree and point out that the “relative allele frequencies” recited in claim 1 are clearly defined in the specification of the instant application as indicating “the proportion of reference and alternate alleles” (see, e.g., paragraphs [00126]-[00130] and claim 48), a teaching not present in Barcellos *et al.* In addition, the Office Action cites the use of biallelic markers to

calculate power for highly polymorphic microsatellites as an alleged teaching of the use of biallelic markers as in claim 27. Applicants once again disagree and submit that claim 1 (amended to incorporate the limitations of original claim 27, now canceled) teaches the characterization of a biallelic polymorphism as being associated with a phenotypic characteristic of interest. It is well known to those of ordinary skill in the art that the microsatellite markers used in Barcellos *et al.* are not biallelic markers. The only use of biallelic polymorphisms described by Barcellos *et al.* is the use of a biallelic marker system to determine power for nuclear family-based and case-control data, but they do not teach the characterization of biallelic polymorphisms as being associated with a phenotypic characteristic of interest as is taught by the instant invention.

To attempt to overcome the deficiencies of the primary reference, the Examiner has combined Barcellos *et al.* with Webster *et al.* and Kroll *et al.* The deficiencies of Webster *et al.* have been discussed above and are incorporated in response to this rejection, as well. The Office Action alleges that the “allele frequency intensity blocks comprising a multitude of intensity patterns” of Webster *et al.* are equivalent to the further first and further second measures of the instant invention. Applicants respectfully disagree and once again point out that the first and second measures of the present invention are derived from first and second samples from case and control groups, respectfully. Therefore, Webster *et al.* does not teach this limitation of the claimed invention since Webster *et al.* does not describe case and control groups. At best, Webster *et al.* compares gene expression measures to a baseline measure, but does not analyze measures from case and control groups of individuals. Further, the Office Action alleges that Kroll *et al.* “teach robust method for comparing measurements from gene expression data,” but Applicants respectfully point out that the purpose of Kroll *et al.* is not to compare gene expression data measurements, but rather to compare *normalisation methods* for gene expression data (Abstract; p. 1, column two, first full paragraph). Although the various normalisation methods compared comprise statistical analyses that are described in the instant application and claims, their use in Kroll *et al.* in normalisation methods is not

analogous to their use in the instant invention, e.g., for determining averages of intensities of signal measurements. Normalisation adjusts measured data so that “subsequent comparison reveals only biological differences relevant for the scientific question being addressed” (p. 1, column one, Introduction). In other words, it serves a correction or quality control function, but is *not* a method for *comparing* different sets of data. Therefore, Applicants respectfully submit that Kroll *et al.* does *not* teach methods for comparing measurements from gene expression data as alleged in the Office Action, and that neither Webster *et al.* nor Kroll *et al.* overcome the deficiencies of the primary reference. In light of the foregoing, Applicants respectfully submit that Barcellos *et al.*, Webster *et al.*, and Kroll *et al.*, whether alone or in combination, do not present a *prima facie* case of obviousness and respectfully request withdrawal of the instant rejection of claim 1 and all claims dependent thereon.

Claims 78-83 were rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Barcellos *et al.* (Am. J. Hum. Genet., 1997, Vol. 61, p. 734-747) in view of Webster *et al.* (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll *et al.* (Nucleic Acids Research, 2002, Vol. 30, No. 11, p. 1-6), in further view of MathWorld (<http://mathworld.wolfram.com/Pairedt-Test.html>, © 1999 CRC Press LLC, p. 1-2) and The 2002 County Loan Rate Calculation Procedure (2002, p. 1). Applicants respectfully traverse all of the above rejections. Applicants respectfully submit that the cited references fail to teach the claimed invention since they do not disclose all elements of the claimed invention for the reasons that follow.

The deficiencies of Barcellos *et al.*, Webster *et al.*, and Kroll *et al.* have been discussed above and are incorporated in response to this rejection, as well. Applicants respectfully submit that neither MathWorld nor The 2002 County Loan Rate Calculation Procedure overcome the previously recited deficiencies of Barcellos *et al.*, Webster *et al.*, and Kroll *et al.* since none of these references, whether alone or in combination, teaches inputting into a computer system relative allele frequencies at an interrogation position that contains a

biallelic marker derived from a first and second sample from a case and control group, respectively; analyzing in the computer system the first and second measures; and characterizing the interrogation position as being associated with a phenotypic characteristic of interest. In particular, claim 75 (from which all instantly rejected claims depend either directly or indirectly) teaches a method of claim 1 “wherein the step of inputting the first measure includes inputting a plurality of first measures, and the step of inputting the second measure includes inputting a plurality of second measures.” As noted above, neither Barcellos *et al.*, Webster *et al.*, nor Kroll *et al.* teaches the limitations of this claim because the “allele frequency intensity blocks comprising a multitude of intensity patterns” of Webster *et al.* are not equivalent to the further first and further second measures of the instant invention because the first and second measures of the present invention are derived from first and second samples from case and control groups, respectively. Since neither the MathWorld website nor The 2002 County Loan Rate Calculation Procedure compensates for this deficiency of Barcellos *et al.*, Webster *et al.*, and Kroll *et al.*, the combination of cited references does not teach each and every element of the claimed invention and therefore cannot constitute a *prima facie* case of obviousness for the rejected claims.

Claims 78 teaches that the “analyzing” of claim 1 includes “pairing a measure from the plurality of first measures and a measure from the plurality of second measures based on common experimental conditions.” The Office Action alleges that Webster *et al.* teaches this limitation in paragraph [0185], but Applicants respectfully disagree and once again note that Webster *et al.* does provide any teaching for first and second measures that are derived from first and second samples from case and control groups, respectively, as recited in claim 1 as currently amended (from which claim 78 depends indirectly). In contrast to the present invention, paragraph [0185] describes a computer system receiving scan data from perfect match and mismatch probes “from *the* experimental biological sample” [emphasis added], for use in background correction, and does not teach that the data is derived from both case and control groups or that a measure from the case group is paired with a measure from the

control group based on common experimental conditions, as taught by claim 78. In fact, none of the cited references teach the method of claim 78. As such, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 79 teaches that the “analyzing” of claim 1 includes “analyzing using a set of differences of paired measures using a method selected from the group comprising: a paired t-test; calculating an Olympic average; determining the median value; and all members of the set having the same sign.” “Paired measures” are determined by pairing individual case and control relative allele frequency measures based on details of the experiment by which the individual measures were obtained (e.g., [00231] and claim 78). Since none of the cited references teach paired measures in accordance with the teachings of the instant specification and claims, none of the cited references, whether alone or in combination, present a *prima facie* case of obviousness for the limitations of the present claim. As such, Applicants respectfully request reconsideration and withdrawal of the instant rejection of claim 79.

With regards to claim 80-83, claim 80 teaches that the “analyzing” of claim 1 includes “calculating the mean of the plurality of first measures and the mean of the plurality of second measures.” The Office Action alleges that Figure 19 of Webster *et al.* provides a disclosure of the elements of claim 80. Applicants respectfully disagree and note that Figure 19 “shows a flowchart of a process of determining if a gene is expressed” ([0143]), but does not include a step at which the mean of a plurality of first measures (derived from samples collected from a case group) and the mean of a plurality of second measures (derived from samples collected from a control group) is calculated. At best, at step 975 of Figure 19, “Once all the pairs [mismatch and perfect match] of probes have been processed and the expression of the gene indicated, an average of ten times the LR_s is computed at step 975” ([0169]). An “LR” disclosed by Webster *et al.* is “calculated by the log of the quotient of the hybridization intensities of the pair (I_{pm}/I_{mm}),” wherein the “pair” consists of one perfect match (pm) probe and one mismatch (mm) probe) ([0148]). In contrast, a mean of instant claim 80 is a mean of a plurality of measures of relative allele frequencies, not an average of “ten times the LR_s” as

disclosed in Webster *et al.* “Relative allele frequencies” as taught by the instant specification indicate “the proportion of the reference and alternate alleles” at an interrogation position (e.g., [00125]-[00126] and claim 48). Therefore, the “average” computed by Webster *et al.* (i.e., an average of ten times the LR_s) is not equivalent to a “mean” of measures of relative allele frequencies as taught by the instant invention. Since none of the cited references teach calculating means of pluralities of measures of relative allele frequencies in accordance with the teachings of the instant specification and claims, none of the cited references, whether alone or in combination, present a *prima facie* case of obviousness for the limitations of the present claim. Accordingly, Applicants respectfully request withdrawal of the instant rejection of claim 80, as well as claims 81-83, which depend therefrom.

In addition, Applicants respectfully question the appropriateness of the combinations of The 2002 County Loan Rate Calculation Procedure with Barcellos *et al.*, Webster *et al.*, and Kroll *et al.* One of the requirements for establishing a *prima facie* case of obviousness is that the “references must be either in the field of the inventor’s endeavor or reasonably pertinent to the specific problem with which the inventor was involved.” (*See In re Deminski*, 796 F.2d 436, 442, 230 USPQ 313, 315 (Fed. Cir. 1986). In other words, the Federal Circuit requires more than a general relationship between fields of the prior art patents, and the art of the references must be analogous to the art of the present invention. The Federal Circuit in *In re Clay* (966 F.2d 656, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992)) said that “[a] reference is reasonably pertinent if . . . it is one which, because of the matter with which it deals, logically would have commended itself to the inventor’s attention in considering his problem. . . . If a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem. . . [I]f it is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it.” Further, in Wang Lab., Inc. v. Toshiba Corp. (993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993)), the Federal Circuit found that low cost memory chips designed for consumers were not analogous to expensive memory chips

designed for industrial applications. The two patents at issue in Wang were not in the same *field of endeavor* merely because they both dealt with memory chips.

Applicants respectfully submit that although both The 2002 County Loan Rate Calculation Procedure and the present specification disclose methods that involve calculating Olympic Averages, the methods of The 2002 County Loan Rate Calculation Procedure are not in the same field of endeavor and are therefore not analogous or reasonably pertinent to the methods of the present invention. Applicants respectfully point out that the purposes of the present invention and The 2002 County Loan Rate Calculation Procedure are completely different. The 2002 County Loan Rate Calculation Procedure states that its goal is to “Increase market orientation and reduce loan program distortions” (p. 1, line 3), as contrasted with the purpose of the present invention, which is laid out clearly in the first sentence of paragraph [0043] as “characterization of nucleic acid sequences.” Further, the methods used in The 2002 County Loan Rate Calculation Procedure are completely dissimilar as compared to those of the instant specification. The 2002 County Loan Rate Calculation Procedure includes steps including “(1) Obtain National Loan Rate (NLR),” “(2) Calculate 2-year Avg PCP,” and the like, but does not include any of the steps recited in the claimed invention. Only impermissible hindsight would transform The 2002 County Loan Rate Calculation Procedure into a *prima facie* obviousness reference for a computer-implemented method for characterizing an interrogation position. An ordinary practitioner seeking methods for storage of reaction cocktails would have no reason to consider The 2002 County Loan Rate Calculation Procedure as a means for doing so, and no such motivation is provided by any of the references cited by the office action. As such, Applicants submit that the divergent interests and purposes of The 2002 County Loan Rate Calculation Procedure and the methods of the present invention would have likely prevented an ordinary practitioner from considering The 2002 County Loan Rate Calculation Procedure when seeking to characterize an interrogation position. Thus, because the purpose directed at each method is substantially different, the Applicants believe that the ordinary practitioner would not have used The 2002

County Loan Rate Calculation Procedure to arrive at the present invention, and respectfully submit that this reference is an improper reference under 35 U.S.C. § 103(a).

Claims 69, 72, 76-78, 80, 81, and 84 were rejected under 35 U.S.C. 103(a) as allegedly being made obvious by Barcellos *et al.* (Am. J. Hum. Genet., 1997, Vol. 61, p. 734-747) in view of Webster *et al.* (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll *et al.* (Nucleic Acids Research, 2002, Vol. 30, No. 11, p. 1-6), in further view of Excoffier *et al.* (Mol. Biol. Evol., 1995, Vol. 12, No. 5, p. 921-927) and Walter *et al.* (Antimicrobial Agents and Chemotherapy, Jan. 2002, Vol. 46, No. 1, p. 89-94). Applicants respectfully traverse all of the above rejections. (Applicants respectfully note that although claim 80 was not included in the listing of rejected claims in the Office Action, the arguments made by the Examiner regarding this claim make clear that this was simply an oversight, so Applicants have added this claim to the claim listing above.) Applicants respectfully submit that the cited references fail to teach the claimed invention since they do not disclose all elements of the claimed invention for the reasons that follow.

The deficiencies of Barcellos *et al.*, Webster *et al.*, and Kroll *et al.* have been discussed above and are incorporated in response to this rejection, as well. Applicants respectfully submit that neither Excoffier *et al.* nor Walter *et al.* overcome the previously recited deficiencies of Barcellos *et al.*, Webster *et al.*, and Kroll *et al.* since none of these references, whether alone or in combination, teaches inputting into a computer system relative allele frequencies at an interrogation position that contains a biallelic marker derived from a first and second sample from a case and control group, respectively; analyzing in the computer system the first and second measures; and characterizing the interrogation position as being associated with a phenotypic characteristic of interest. The specific rejections of claims 69, 72, 76-78, 80, 81, and 84 are now addressed in turn.

Claim 69 provides an equation for correcting the first and second measures of relative allele frequency. The Office Action alleges that the limitations of claim 69 are

disclosed by Excoffier et al. at p. 922, column one, paragraph three and in equation (3).

Applicants respectfully disagree and submit that both the purpose and methods of Excoffier are different than that of the instant invention. The method of claim 69 *corrects relative allele frequencies* based the equation: $P_i \approx \sum_{j=1}^N m_{ij} f_j$, where “where P_i is a corrected relative allele

frequency of the interrogation position; N is the total number of different haplotype patterns within the haplotype block; m_{ij} is a coefficient having a value of +1 if the allele at position i in haplotype pattern j matches a reference allele of the SNP and having a value of 0 if the allele at position i matches an alternate allele of the SNP; and f_j is a haplotype pattern frequency.” In

contrast, the methods of Excoffier *et al. derive estimates of haplotype frequencies* using a set of equations, none of which are the equation of claim 69. For example, “ P_j ” in equation (3)

noted in the Office Action is a probability of the j th phenotype and is given by the sum of the probabilities of each of the possible c_j genotypes, $P_j = \sum_{i=1}^{c_j} P(h_k h_l)$, where $P(h_k h_l)$ is the

probability of the i th genotype made up of haplotypes k and l , $P(h_k h_l) = p_k^2$ if $k = l$, and $P(h_k h_l) = 2p_k p_l$ if $k \neq l$, where p_k and p_l are the population frequencies of the k th and the l th haplotypes

(p. 922, column one, last paragraph and column two, first paragraph). Therefore, not only are the purposes of the methods of Excoffier different from those of the instant application, terms present in the equation of claim 69 (e.g., a corrected relative allele frequency (P_i), a total

number of haplotype patterns in a haplotype block (N), and a coefficient depending on the genotype of an allele at an interrogation position (m_{ij})) are not even present in equation (3). In

addition, Excoffier defines a “phenotype” as “a multilocus genotype whose haplotype phase is unknown a priori,” and a “genotype” is “defined as a particular combination of two multilocus haplotypes” (p. 922, first paragraph, second full paragraph), which is completely different

from the way these terms are used in the instant specification, further underscoring the differences between the methods of Excoffier and those of the instant invention. Since neither Excoffier nor any of the other cited references teaches the equation of claim 69, these references, whether alone or in combination do not teach each and every element of the

claimed invention and therefore do not present a *prima facie* case of obviousness. As such, Applicants respectfully request withdrawal of the instant rejection of claim 69.

Claim 72 teaches a method of claim 1 in which a difference between the first measure of relative allele frequency and the second measure of relative allele frequency is calculated. Equation (10) in Excoffier *et al.* is alleged to describe the limitations of claim 72, but, in fact, equation (10) describes something entirely different. Equation (10) is a means for using the “similarity index I_F ” defined as the proportion of haplotype frequencies in common between estimated and true frequencies to examine how close estimated haplotype frequencies are to actual haplotype frequencies (p. 924, column one, first full paragraph). In other words, equation (10) compares actual to estimated haplotype frequencies as a means to determine the accuracy of the haplotype frequency estimation methods described by Excoffier *et al.* This is completely different from the method of claim 72 for many reasons, not the least of which is that Excoffier does not calculate a difference between first and second measures of relative allele frequencies as recited in the instant claim. As such, Applicants respectfully submit that the cited references do not teach each and every aspect of the claimed invention and respectfully request that the rejection of claim 72 on this basis be withdrawn.

Claim 77 teaches a method of claim 1 “wherein said interrogation position is a plurality of interrogation positions in the same or different nucleic acid segments, and for each interrogation position a said first measure of allele frequency and a said second measure of allele frequency are inputted into said computer system and analyzed to characterize said each interrogation position.” In discussion of claim 77, it was alleged that Excoffier provides “polymorphisms simulated using four allele positions [p.923, Col. 2, ¶2], as in instant claim 77.” However, Applicants respectfully submit that “polymorphisms simulated using four allele positions” does not teach the limitations of claim 77. In the paragraph indicated by the Examiner, Excoffier *et al.* provide a way to test the effectiveness of the EM algorithm in inferring haplotype frequencies, but do not describe a method for characterizing a plurality of interrogation positions comprising inputting into a computer system a first and second

measure of allele frequency as is taught by claim 77. As such, Excoffier does not teach the limitations of claim 77, and since none of the other cited references teach these limitations the combination of these references does not render the instant invention obvious. As such, Applicants respectfully request withdrawal of the instant rejection of claim 77.

Claim 75 (from which claims 76, 78, 80, 81, and 84 depend either directly or indirectly) teaches a method of claim 1 “wherein the step of inputting the first measure includes inputting a plurality of first measures, and the step of inputting the second measure includes inputting a plurality of second measures.” As noted above, neither Barcellos *et al.*, Webster *et al.*, or Kroll *et al.* teaches the limitations of this claim because the “allele frequency intensity blocks comprising a multitude of intensity patterns” of Webster *et al.* are not equivalent to the further first and further second measures of the instant invention because the first and second measures of the present invention are derived from first and second samples from case and control groups, respectively. Since neither Excoffier *et al.* nor Walter *et al.* compensates for this deficiency of Barcellos *et al.*, Webster *et al.*, or Kroll *et al.*, the combination of cited references does not teach each and every element of the claimed invention and therefore cannot constitute a *prima facie* case of obviousness for the rejected claims. In light of the foregoing, Applicants respectfully request its reconsideration and withdrawal of the instant rejection of claims 76, 78, 80, 81, and 84.

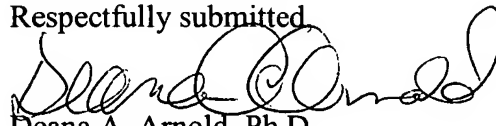
The citation of Walter *et al.* as allegedly providing the motivation to combine the art in the instant rejection is acknowledged and respectfully traversed. Applicants can find no such motivation in Walter *et al.*, and the portion of this reference indicated by the Examiner to provide such motivation (p. 923, Col. 2, ¶4) does not exist in this reference, which spans pages 89-94, as recited above. As such, Applicants respectfully request that the Examiner specifically point out where in Walter *et al.* lies the motivation to combine the references recited in the instant rejection, or withdraw the instant rejection.

Additional Claim Amendments

Claims 3-5 were amended to correct antecedent basis by making them depend from claim 1 and by substituting the terms "case" and "control" for the terms "first" and "second," respectively. Claims 17, 20, 22-24, and 26 were amended to correct antecedent basis by substituting the terms "case" and "control" for the terms "first" and "second," respectively. Claims 110 and 111 were amended to correct antecedent basis by inserting "the plurality of" before "intensities" as recited in claim 108 from which they depend. Claim 135 was amended to depend from claim 133 rather than claim 134, which was canceled herein. Claims 1, 14, 16, 48, 76, 98, 108, and 110 also had additional minor grammatical changes. No new matter was introduced by virtue of these amendments, which are both fully supported by and implicit within the specification and claims as originally filed.

For the reasons set forth above, Applicants believe all claims now pending in this Application are in condition for allowance. If any fees are due in connection with the filing of this response, the Commissioner is hereby authorized to charge such fees to Deposit Account 50-2043. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-625-4603.

Respectfully submitted



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